Hepatitis Viruses

Introduction

The hepatitis viruses are not a family in the typical taxonomy of viruses. They are a grouping of viruses that cause **inflammation of the liver**, that cause **hepatitis** (hepatocyte-itis). They are taught together only because of their symptoms. Some of these viruses cause **acute hepatitis** and do not cause chronic infections. Some of these viruses cause **chronic hepatitis** and do not present with much of an acute picture. Symptoms of hepatitis virus represent the immune destruction of the hepatocytes with virus.

Acute infections occur because the immune system does a great job of eradicating the virus and infected cells. The virus gets into hepatocytes, the cells of the liver. The host immune system drops a nuke that eradicates the virus . . . and the cells it was in. Acute infections are generally pretty obvious. When hepatocytes die they release **aminotransferases** into the bloodstream. The alanine aminotransferase and the aspartate aminotransferase (**ALT** and **AST**) levels rise, and are the markers of acute hepatocellular injury. The patient may become **jaundiced** from impaired ability to metabolize bilirubin. The acute infection ends, and symptoms resolve. Hepatitis A is the virus of acute infections.

Fulminant hepatic failure is an extreme form of acute infection. Not only do the AST and ALT rise and the person becomes jaundiced, but the liver fails entirely. A rise in the **INR** and the presence of **hepatic encephalopathy** in a previously healthy liver is a marker of fulminant hepatic failure. This is how hepatitis viruses kill. Without a transplant, the patient dies. Fulminant hepatic failure is caused by hepatitis D often and hepatitis E rarely. Fulminant hepatic failure occurs most commonly in an already diseased liver (see GI: Hepatobiliary #18: *Cirrhosis*).

Chronic infections occur because the immune system does a poor job of eradicating the virus and infected cells. The virus continues to replicate in the hepatocytes. The immune system recognizes the infected hepatocytes and tries to eradicate the infection. This tug-of-war of replication and destruction provides a smoldering inflammatory state. There are no symptoms felt by the patient day to day, and the laboratories don't show anything is wrong with the liver. Until . . . Chronic smoldering inflammation throughout the liver is what provokes **cirrhosis,** fibrosis from long-standing inflammation. Inflammation not only causes scarring, but it also provokes malignant transformation. Chronic infections provoke cirrhosis and **cancer**, particularly hepatocellular carcinoma. Chronic infection, Cirrhosis, and Cancer. Hepatitis C is the chronic hepatitis infection.

There are five hepatitis viruses you should be aware of. Hepatitis A and E are the mild acute hepatitis viruses, except when E infects pregnant mothers, where the mortality rate is 20%. Hepatitis C is the chronic hepatitis virus that results in cirrhosis then cancer. Hepatitis B can end up as both an acute infection (in immunocompetent hosts) or a chronic infection (in immunocompromised hosts). Hepatitis D is both Dumb and Deadly, causing fulminant hepatic failure but requiring the presence of hepatitis B to replicate.

We're going to cover each of the hepatitis viruses in this lesson. We will spend a significant portion on interpretation of hepatitis B serologies, as this is commonly tested. We talk about treatment in Viruses #8: *Antivirals*. If you know Table 7.1, you will have success with hepatitis viruses. If you are able also to master Table 7.2, you have the topic covered. This lesson gets you through the details so the take-aways stick.

	HEPATITIS A	HEPATITIS B	HEPATITIS C	HEPATITIS D	HEPATITIS E
OME name	Acute hepatitis	Both hepatitis	Chronic hepatitis	Deadly hepatitis	
Spread	Fecal-oral	Sex and blood	Blood	Sex and blood	Fecal-oral
Envelope	Naked	Enveloped	Enveloped	Enveloped (steals B's)	Naked
Infxns	Acute mild infxn	Severe acute infection (competent)	Chronic, cirrhosis, cancer	Fulminant hepatitis	Acute mild infxn
	No exceptions	Chronic infection (compromised)	No exceptions	Chronic infection	Pregnant = fulminant
Family and structure	Picornavirus ss(+)RNA Icosahedral	Hepadnavirus Incom dsDNA Icosahedral	Flavivirus ss(+)RNA Icosahedral	Dysfunctional ss(+)RNA codes one gene	Calicivirus ss(+)RNA Icosahedral
Vaccine	Vaccine + (killed)	Vaccine + (particle)	No	No	No
Where seen	US contaminated foods	Asia = Vertical US = Sex	US = Needles	US = Sex	Third-World pregnant women
Treatment	N/A	Treat with antiretrovirals	Treat to cure with polymerase inhibitors	N/A	N/A
		Do not use pegylated interferon and ribavirin	Do not use pegylated interferon and ribavirin		

Table 7.1: Summary Table of the Hepatitis Viruses

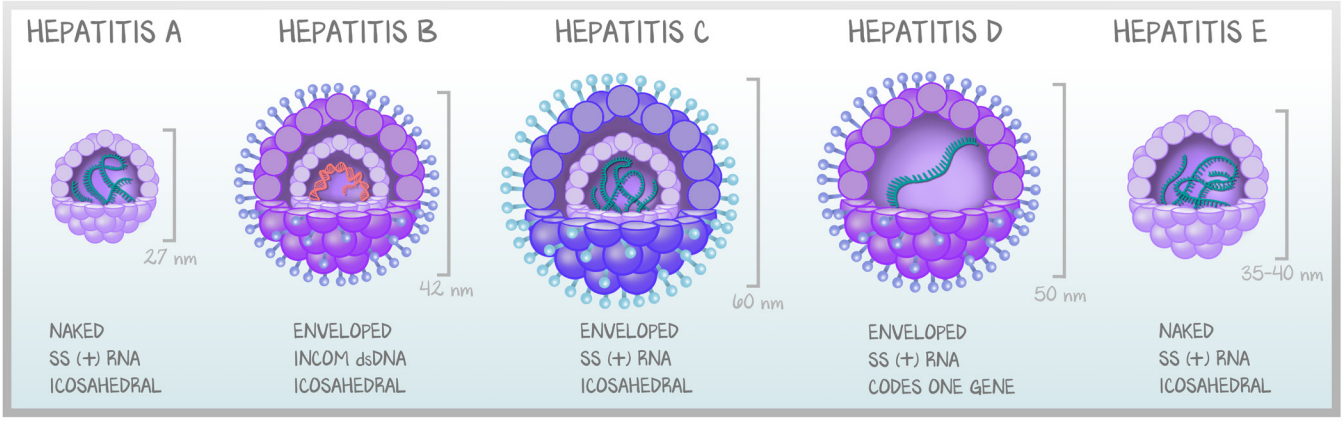

Figure 7.1: Comparison of Hepatitis Virions
Hepatitis viruses are very dissimilar. They are only linked together because of their symptomatology—causing hepatitis. This illustration is used as a visual que as we begin a discussion of each within this lesson.

Hepatitis A (Hep A)

Hepatitis A (aka Hepatitis Acute) causes only **acute hepatitis**. It is a picornavirus and is also an enterovirus (Viruses #4: *ss(+) RNA Viruses*). Picornaviruses are single-stranded, positive-sense RNA viruses that are also naked. Being naked necessitates that Hep A be icosahedral. Being a naked virus, it is resistant to heat, organic solvents, and gastric acid. Therefore, because it can exist outside the human host, it can be and is transmitted via the **fecal-oral** route. Hep A is highly contagious and spread by contaminated food and fomites. An infected person has diarrhea, then takes fecal material from their butt and places it on your food. Contaminated food infects you when ingested. Just like the other enteroviruses, hepatitis A replicates in the oropharynx, then goes viremic unless antibodies are present. Early in the disease course the virus causes a **diarrheal illness**. After an incubation period of about 2 weeks, the patient presents with **liver damage** (hepatitis). The "liver damage" is rarely fulminant, and will be expressed only as a modest rise (few hundreds) of AST and ALT. Most patients do not get jaundiced. Most people don't have any symptoms except for the diarrhea. Their enzymes are elevated, but the patient is unaware of this. There is no risk of carrier or chronic state, as it is only acute and is a **self-limiting** disease. After exposure, the patient is immune. A **vaccine** is available (killed-virus) and all patients should be vaccinated.

Hepatitis B (Hep B)

Hep B is a hepadnavirus(hepa-DNA-virus), the hepatitis virus made of **DNA**. It is an **incomplete double-stranded DNA**—some of the DNA is ss, but most of the DNA is dsDNA. It is the only DNA hepatitis virus. Even though it is a DNA virus, it does not follow the rules of DNA viruses (lesson #3: *DNA Viruses*). It is icosahedral, and (mostly) double-stranded, but it replicates in the cytoplasm and does not use host DNA polymerase to replicate (the next section is dedicated to these differences). Hepadnavirus Has an envelope. Having an envelope means that it is not resistant to heat, gastric acid, or detergents, and therefore cannot be transmitted fecal-oral or survive outside the human host. It is transmitted through **blood**, **sex**, and **vaginal birth**. The highest incidence of Hep B is in Southeast Asia, with **vertical transmission** the most common cause. We have a **vaccine** for Hep B (which is secreted conglomerates of surface antigen).

Hep B can be **both** acute and chronic. That is because **symptoms correlate to immune reactivity** (the virus doesn't kill your liver; your immune system kills your liver trying to kill the virus).

If the immune system is robust and Hep B is contracted, there is a higher chance of acute hepatitis symptoms (jaundice; AST and ALT elevation) but also a higher chance of clearing the infection, to escape the carrier state. **Severe symptoms from a good immune system is likely to clear the virus.** After exposure and clearance, the patient is immune.

If the immune system is weak (neonates in particular, especially vertical transmission, transplant, AIDS), then there will be a weak immune response, no liver damage, but the virus will not clear. **Mild symptoms from a poor immune system becomes a chronic carrier.** Chronic carriers will have it always, are infectious, and have increased risk of developing hepatocellular carcinoma even **without** cirrhotic changes. Chronic hepatitis B does result ultimately in cirrhosis. In the carrier state, antibodies of immunity do not form while antibodies to Hep B antigens do form (discussed next).

Hepatitis B Virion and Replication

The viral genome is **circular** DNA. The genes the genome codes for are overlapping—where transcription starts on the circle determines the size of the transcript. One transcript is for the **capsid proteins**, called the hepatitis B **core antigen**, abbreviated **HBcAg**. An in-frame reading of that same gene gives rise to a variant of the HBcAg called the hepatitis B **e antigen**, abbreviated HBeAg, which is secreted by cells. Another transcript codes for a glycoprotein in the virion envelope, called the hepatitis B **surface antigen**, abbreviated HBsAg. The final gene transcript is a single continuous string of mRNA that is **larger than the genome itself**.

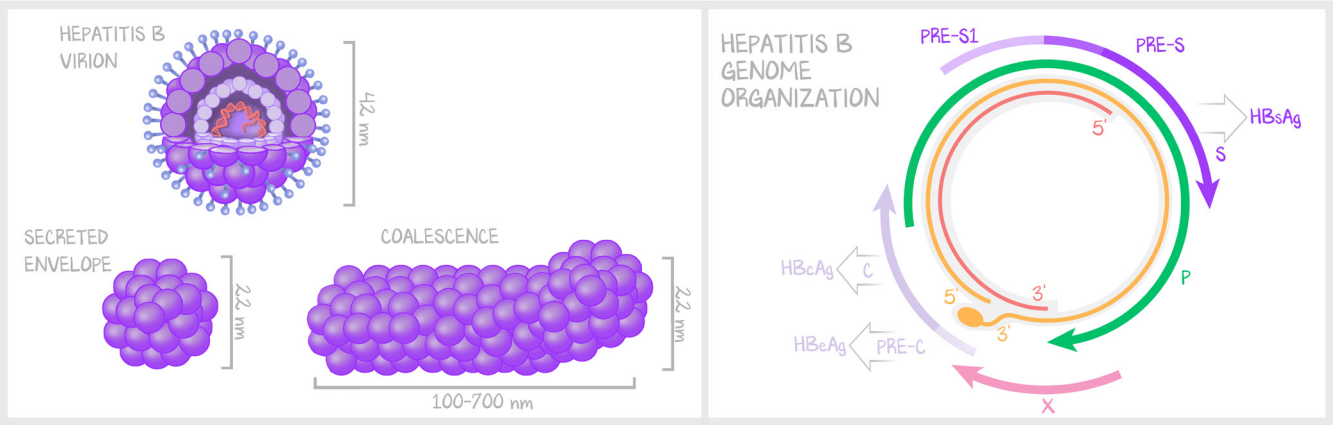

Figure 7.2: Hepatitis B
Hepatitis B is an enveloped virus. Sometimes it secretes envelopes without a capsid contained. These coalesce to form large conglomerates of envelope protein, perfect for developing a vaccine. The hepatitis B genome is circular, with different gene products depending on the start. The same string of nucleotides can code for HBcAg, used in the capsid, as the nucleotides for HBeAg, useless secreted protein. HBeAg is made along with the transcription start. Much of the illustration is accurate. What you need to know is, some of the orange DNA codes for HBsAg, some codes for HBcAg and HBeAg, and the transcript used for replication by reverse transcriptase is longer than the genome itself.

Normal virions contain **HBcAg** proteins, the DNA genome, and are enveloped in plasma membrane with the glycoproteins **HBsAg** in the envelope. Active infection with hepatitis B will demonstrate the presence of these antigens.

Hepatitis B gets too excited sometimes. When the gene for HBcAg (which is core protein and part of the virion) gets read in the wrong reading frame, it makes HBeAg instead of HBcAg. **HBeAg** serves no function to the viral life cycle and is merely an accidental protein synthesized from the improper reading of the genome. The presence of antigen means a current infection. HBeAg, HBsAg, and HBcAg are all markers of current infection.

Hepatitis B gets too excited sometimes. It gets too excited and sometimes makes too many envelopes and releases those empty envelopes without any capsid or genome. Those empty envelopes still have HBsAg in the plasma membrane, but the virion is devoid of virus parts. This allows the envelope-only-particle to be small. Conglomerations of these empty envelopes are called **Dane particles**. Dane particles are a high concentration of HBsAg without any viral genome. High concentration of antigen plus no virus at all sounds like a pretty good way to make a vaccine. The **hepatitis B vaccine** is exactly that—HbsAg without any virus.

Hepatitis B is a DNA virus. But unlike DNA viruses, Hep B encodes a **reverse transcriptase** and replicates through an **RNA intermediate**. The replication occurs in the cytoplasm, inside the capsid. The larger-than-the-DNA-genome mRNA is dispatched from the nucleus into the cytoplasm. There, it is

packaged into the capsid along with reverse transcriptase. Reverse transcriptase reads the mRNA and generates the anti-sense DNA, forming a complementary and antiparallel DNA-RNA hybrid. Reverse transcriptase then clears the mRNA strand, acting as a ribonuclease, leaving a single-stranded DNA. The same enzyme then fills in the positive-sense DNA from the negative-sense template. The DNA is circular, and the polymerase can only move towards the growing strand's 3' end. Just as it is about to finish the complementary and antiparallel strand, the process is interrupted. The processing of the genome occurs in the capsid, while it is being assembled into the envelope. The nucleocapsid is enveloped by the HBsAg-containing endoplasmic reticulum before the strand can be completed. The door shuts before the final string of DNA nucleotides can be built. The result is a single strand of DNA that is completely circular, complementary and antiparallel to another almost-complete single strand of DNA.

Hepatitis B Serologies

You will, without a doubt, be asked to interpret hepatitis B serologies. We go into details here, but if you learn nothing else, learn this paragraph. **Anti-HBs** is a marker of **immunity**. It is the only antibody that confers immunity. If the patient is anti-HBs positive, they are immune and there is no virus in them. The presence of any antigen confirms active infection. Any anti-HBs-positive patient is immune and cannot have virus in them. The only question to answer is whether they got that anti-HBs from a vaccine or from a virus. Antibodies form to other antigens, but they do not convey immunity. If the patient is anti-HBs positive and anti-HBc positive, they are exposed-immune. IF the patient is anti-HBs positive and anti-HBc negative, they are vaccinated immune. If the patient has antigen in them now, you must decide whether they are acutely infected and could clear, or whether they are chronically infected and never clear. If any-antigen-positive and anti-HBc IgG negative, they are acute and can clear. If any-antigen-positive and anti-HBc IgG positive, they have a chronic infection and will never clear.

The rest of this section digs into why and how.

A patient is infected with hepatitis B. For two months (60 days), nothing happens. There are no symptoms, there are no detectable antigens, nor detectable antibodies. Hepatitis B is establishing an infection in the hepatocytes it managed to infect. Around 2 months, virus starts replicating. Because virus is replicating, **antigens are expressed**. Surface antigen (HBs), core antigen (HBc), and HBe antigen are detectable in the blood. The course of the infection has not yet been determined.

Acute = Clearance = Immunity. The immune system notices and mounts an antibody response. The first antibody to become positive is **anti-HBc**. The presence of anti-HBc IgM (IgM is the primary antibody immune response) facilitates the immune system in fighting off the virus. "Fighting off the virus" means "kill hepatocytes infected by virus." The death of the hepatocytes provokes symptoms—jaundice and elevation of the liver enzymes. Around month 4, anti-HBe antibodies form. By this time, anti-HBc IgG has been produced (IgG being the secondary antibody response, an indicator that the infection has been going on for some time). The presence of anti-HBc and anti-HBe antibodies subdues the infection. Liver enzymes return to normal. **Antigen disappears**. At month 6, **anti-HBs** begins to form. Anti-HBs will form only if the virus is cleared. Anti-HBs also confers immunity. The antibody that confers immunity is also a marker that virus was eliminated. If the virus is not cleared, anti-HBs will never form.

When you draw a sample from an immune person, anti-HBs will be present and antigen not. You want to assess how that immunity was conferred. If the patient received a vaccine, which is made only of HBsAg, they will have anti-HBs positive. Their immune system never saw another antigen, so all other antibodies will be negative. If the patient received a virus, which made HBsAg, HBcAg, and HBeAg, and they are now immune and cleared, they have anti-HBs, anti-HBc, and anti-HBe. Having **only anti-HBs** means **vaccinated**. Having **anti-HBs and any other antibody** means **exposed**. Having anti-HBs means immune.

Persistent = Failed Clearance = No Immunity. The immune system notices. Anti-HBc IgM is made. The cell-mediated response to intracellular pathogens is insufficient to clear the virus. Hepatocytes do not die. There is no jaundice, and no elevation of the liver enzymes. The patient may not even know they were infected. Without control, the virus **antigen does not clear**. Because antigen does not clear, anti-HBs will not form. **Anti-HBc and anti-HBe** will continue to fight the present virus. But because there was no clearance of the virus from the initial infection, the virus establishes a persistent infection.

At the time a blood sample is taken, if there is antigen present, there is an infection. But because the exposure is so remote, and the symptoms up to this point nonexistent, the patient doesn't know when they were infected. So the question is: do they still have a chance to clear, or are they in a persistent infection? The only way to tell is with the anti-HBc antibodies. Ongoing serologic evidence of virus past 6 months defines the chronic infection. But you, as the provider, don't know what month the patient is at when you evaluate them. Anti-HBc IgM is the first antibody to form. **Anti-HBc IgG forms around 6 months**. So, if they have antigen and have IgG, they have missed their opportunity to clear, and are in a persistent infection.

FINDING	WHAT IT MEANS	FINDING	WHAT IT MEANS
Anti-HBs	Immunity	HBsAg	Infected
Anti-HBc	Exposed	HBcAg	Infected
Anti-HBe	Exposed	HBeAg	Infected

Table 7.2: Hep B Serology Interpretation Light

SEROLOGIC REACTIVITY	DISEASE STATE					HEALTHY STATE	
	EARLY (PRESYMPTOMATIC)	EARLY ACUTE	ACUTE	CHRONIC	LATE ACUTE	RESOLVED	VACCINATED
Anti-HBc	–	–	+	+	+/–	+	–
Anti-HBe	–	–	–	–	+/–	+/–	–
Anti-HBs	–	–	–	–	+	+	+
HBeAg	–	+	+	+	–	–	–
HBsAg	+	+	+	+	+	–	–
Infectious virus	+	+	+	+	+	–	–

Table 7.3: Hep B Serology Summary Heavy

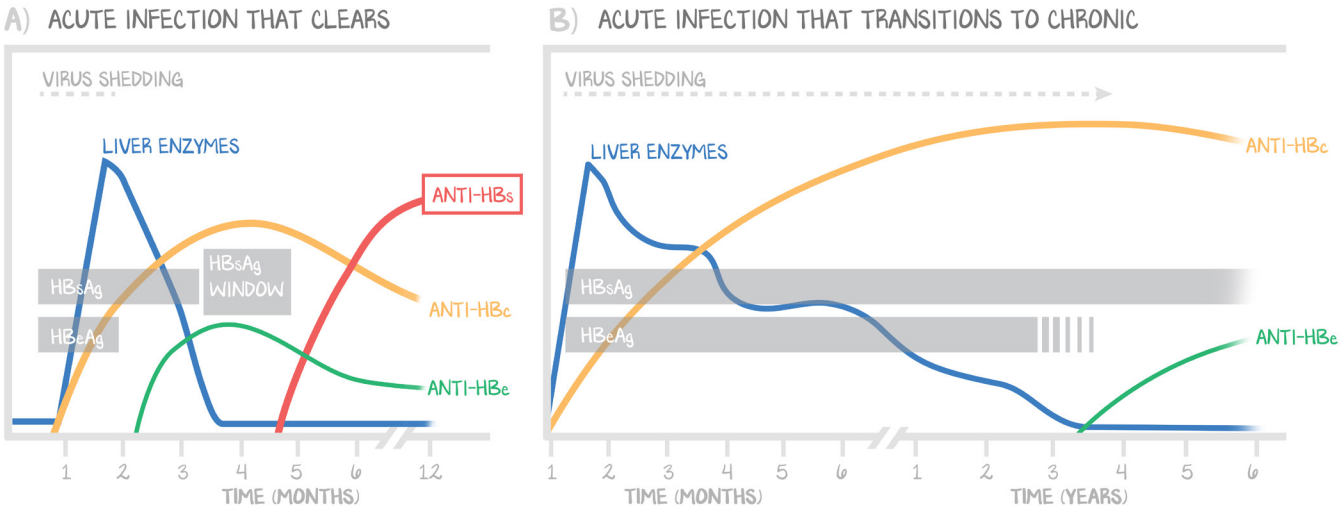

Figure 7.3: Hepatitis Serology Patterns
(a) The natural course of a hepatitis B infection that will clear will show the development of anti-HBs antibodies by month 5. If the antigens clear and anti-HBs forms, the infection will clear and the patient will be immune. (b) The natural course of a hepatitis B infection that will not clear and results in chronic infection will not demonstrate a clearance of HBeAg or HBcAg (no window), and will never develop anti-HBs. Anti-HBs and antigen clearance are synonymous with immunity. The lack of anti-HBs and persistence of antigen indicates chronic infection.

The "window period" that is so famous in Hep B discussions is not the window period for Hep B; it is the window period for **HBsAg ONLY**. When we didn't know about HBc, HBe, or the HBsAg window, we would test people for the HBsAg and the anti-HBs antibody. There is a period of a month or two where neither is positive, yet the patient is infected. We missed chronically infected Hep B patients because of the HBsAg window period. We would not have missed those infections if we had known we could look for the core or e antigen, or if we had known we could look for the anti-HBc or anti-HBe antibodies. Thanks to this blunder, which now cannot possibly be repeated, the board examiners always ask an interpretation question about hepatitis B serologies. Anti-HBc and anti-HBe only signify previous exposure and do not confer immunity. The presence of antigen means actively infected. The presence of anti-HBs means immunity.

Therapeutics for hepatitis B are not as promising as for hepatitis C. **Antiretrovirals** used to treat HIV are being employed to treat chronic hepatitis B infections, targeting the reverse transcriptase. A chronic hepatitis B infection can provoke **hepatocellular carcinoma** or **cirrhosis**. Worse than chronic hepatitis C, a chronic hepatitis B infection can provoke hepatocellular carcinoma even without first developing cirrhosis.

Hepatitis C (Hep C)

Hepatitis C is the only member of the *Hepacivirus* (Hepa-C-virus) genus of the *Flaviviridae* family. Hep C is the Chronic hepatitis virus, and its transmission is blood to blood (blood transfusions before the 1980s, **intravenous needle-sharing** since then). It is not spread through sexual contact (though sexual partners who also do needle drugs will often shoot up together). Ongoing **cell-mediated cytotoxicity** (T cells) trying to clear the virus fails, and only (inevitably) scars the liver. Hepatitis C causes Cirrhosis, and Hepatitis C causes Hepatocellular Carcinoma. The liver is intensely regenerative, but ongoing inflammation over decades leads to cirrhosis. There **are treatments** to **cure Hep C** now. And so, while Hepatitis C remains the Chronic hepatitis virus, it is also the hepatitis virus we can Cure.

Hep C cirrhosis was the inevitable outcome for infected patients. A brutal, year-long treatment with ribavirin and interferon (which makes the patient feel like they have the flu) was available and was largely unsuccessful. Now with the **direct-acting antagonists** (Virus #8: *Antivirals*), Hep C is easily cured.

Hepatitis C is a flavivirus but not an arbovirus. Being a flavivirus, its genome is ss(+)RNA, its capsid is icosahedral, and it is enveloped. Because it has an envelope, it does not resist heat, stomach acid, or detergents, so cannot be fecal-oral.

Hepatitis D (Delta Agent)

"*Hep D makes Hep B whole*," and Hepatitis **D**eath is **D**umb, help recall the relevant details of Hep D. Hep B is an incomplete dsDNA, with some ssDNA exposed. Hep D is **defective ss(+)RNA** that codes for **one protein** (is dumb). Yet this virus is the cause of 40% of fulminant hepatitis viral infections (Hep D = Death). I imagine this little RNA virus "filling in" the nucleotides of the incomplete DNA strand with its RNA, the ss(+)RNA partnering up with the ssDNA to make the two strands whole. This is not the actual mechanism—the Hep D genome does not pair with the Hep B genome—but it helps to remind me that Hep B is incomplete and Hep D relies on Hep B to replicate. Hepatitis D is an enveloped virion but cannot make any envelope proteins. Its envelope is the envelope of hepatitis B. Therefore the attachment, fusion, and exit from the cell must be identical. The only reason why this is possible is because hepatitis B sends out empty envelopes without an infectious element in it. Hep D takes the empty seat. Because it is enveloped, it is not resistant to the environment, and so cannot be transmitted fecal-oral. It is therefore a disease of **sex and blood** transmission.

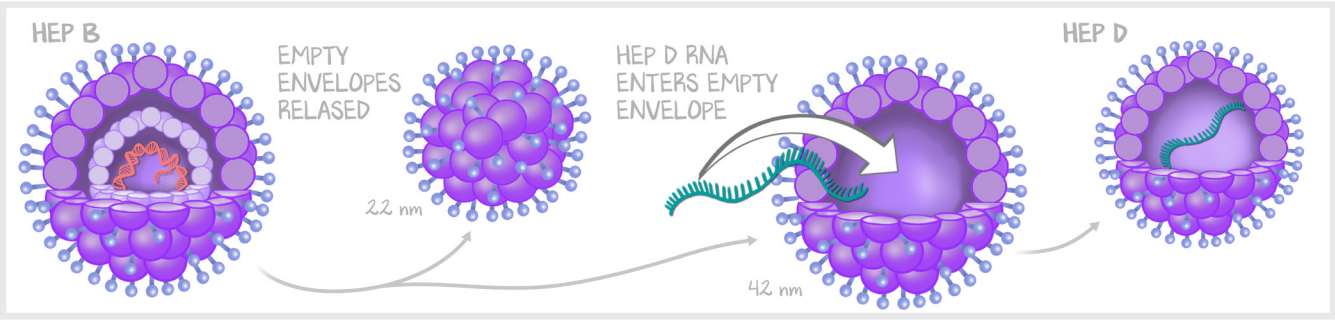

Figure 7.4: Hepatitis D Steals a Ride
Hepatitis B's late genes construct envelopes for its nucleocapsid. Hepatitis B makes so much envelope proteins that some envelopes are released without hepatitis B nucleocapsid. Hepatitis D requires an envelope to survive out of a host cell. Hepatitis D relies on hepatitis B to provide those empty envelopes, and hops a ride in an open seat. This explains why a superinfection, where hepatitis B is already established when hepatitis D infection occurs, is so much worse than infection at the same time. In the early infection, immediate early and early genes coded by hepatitis B are not virion particles and envelopes. In an established infection, late genes are already cranking out envelopes and capsids for hepatitis D to take advantage of.

Any chronically ill liver that gets an acute injury has a higher chance for fulminant hepatic failure than one without chronic illness. Whether that chronically ill liver is because of metabolic disease or a chronic hepatitis virus doesn't matter. An acute infection with one of the acute viruses can be bad. It's worse if there is an already-ill liver. It's worst if the chronic illness is from infection with Hep B, then later, the acute infection is with Hep D. If a patient has Hep B chronically and contracts Hep D, **superinfection with Hep D has the highest risk of fulminant failure**.

Co-infection (Hep B and Hep D at the same) is not as bad as superinfection (chronic Hep B with a superimposed acute Hep D), because hepatitis B must establish its infection before Hep D can replicate.

Hepatitis E

Hepatitis E is usually of no consequence to the United States. It is seen in developing countries. It is calicivirus, like norovirus, so is ss(+)RNA, fecal-oral, and causes diarrhea. Women who are **pregnant** and are in **Third World countries die from Hep E**. Everyone ELSE just gets the diarrhea.